REMARKS

Reconsideration is respectfully requested.

The Examiner is thanked for her courtesy in granting Applicants' Attorney an interview on March 31, 1982, which interview is hereby made of record. The substance of the interview is set out in these remarks. Attached hereto for the Examiner's convenience is a compilation of all the pending claims which was referred to during the interview.

A. Amendments

The allowance of Claims 1-3, 23, and 24 is gratefully acknowledged. It is also believed that Claims 27 and 28 should also be allowable without amendment since they depend from allowed Claims 23 and 24.

Applicants have cancelled method Claims 15-18 in order to advance the prosecution of the present application, although not completely agreeing with the Examiner's characterization of these claims. Moreover, Claims 25 and 26 have been amended to make them product-by-process claims equivalent to Claims 29 and 30, and Claims 29 and 30 have been cancelled. It is believed that Claims 25 and 26 are allowable as amended.

B. Claims 22 and 31

The only outstanding issue regarding the claims as amended is the rejection of Claims 22 and 31 under 35 USC 112 (first paragraph) and 35 USC 103. These rejections are respectfully traversed.

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1) Rejection under 35 USC (first paragraph)

The first paragraph of Section 112 requires that the specification as a whole enabled the making and using of the claimed antibody by a person skilled in the biological arts. It is respectfully submitted that Applicants have in fact done so with regard to the antibody claimed in Claims 22 and 31, and that they are therefore entitled to claims of such scope.

Claims 22 and 31 are directed to a class of antibody having the characteristics set out in the claims. That is, both rejected claims cover complement-fixing mouse monoclonal antibody which reacts with essentially all normal human peripheral T cells but not with normal human peripheral B cells, null cells, or macrophages. This antibody is "selectively described by the parameters of the disclosure" by the characteristics described above, although the rejected claims certainly do not contain all of the parameters set out in the application. Applicants have taught how to prepare antibodies within the scope of the claim. It is respectfully submitted that no more is required by 35 USC 112 (first paragraph).

Applicants recognize that each hybridoma produces a single antibody having a particular specificity. That is, after all, the purpose for making hybridoms in the first place. It is not believed, however, that this fact warrants the rejection of Claims 22 and 31. The Examiner has asserted that it is "doubtful" that antibody produced by one hybridoma is "the same" as antibody produced by another hybridoma or recognizes all of the same antigenic sites.

First, it is respectfully submited that this unsupported doubt is not sufficient basis for rejection of the

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claims. If the Examiner has support for her statement, she is respectfully requested to make it of record so that Applicants' Attorney may properly respond.

Second, accepting for purposes of argument that antibodies within the scope of Claims 22 and 31 may not be identical to each other, this fact is not seen to support the outstanding rejection. Antibodies may differ in many ways while still recognizing the same antigen. That is, parts of the antibody not related to the biding site (where the antibody combines with the antigen) may vary. Certainly such variations should not remove an antibody from the scope of the present invention.

Third, accepting for purposes of argument that antibodies within the scope of Claims 22 and 31 may not recognize the same antigenic sites, this fact is also not seen to support the outstanding rejection. The claimed class of antibodies recognizes an antigenic site (or sites) specific for normal human T cells, which site (or sites) is not found on normal human peripheral B cells, null cells, or macrophages. Moreover, the claimed class of antibodies binds complement. Any mouse monoclonal antibody which recognizes this site or sites or an equivalent site specific for normal human T cells and which fixes complement is included within Applicants' invention and is therefore within the legitimate scope of protection which they should receive.

Having described the specificity of the claimed antibody in such full, clear, concise, and exact terms as to enable any person skilled in the art to make and use the same, Applicants have complied with the requirements of the first paragraph of 35 U.S.C. 112. Since Applicants were the first to

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discover the class of antibodies covered by rejected Claims 22 and 31, it is respectfully submitted that they are entitled to claims of this scope so that they prevent others from reaping the fruits of their invention.

During the interview, the Examiner questioned whether Applicants were entitled to claims which are not limited to a particular method of preparing the antibody. As discussed during the interview, this reason is not believed to support rejection of these claims. Having enabled production of the claimed antibody by one method, Applicants are entitled to claims to the antibody regardless of how prepared. By analogy to the chemical arts, one who invents a new chemical compound is entitled to a claim to the compound itself, assuming other criteria for patentability are met. If a later inventor devises a second way of preparing this compound, he may get a claim to his method. But this method claim will be subservient to the original inventor's compound claim. The same result should obtain in the present situation.

Whether other methods do or do not produce the same antibody is respectfully submitted to be irrelevant. Applicants are not claiming these other methods but rather the class of antibody which they have described and for which they have provided a method of production.

2) Rejection under 35 USC 103

The Examiner has also rejected Claims 22 and 31 as being obvious under 35 USC 103 from the Williams, Lampson or McMichael references, which the Examiner states "show hybridoma preparation and antibodies which react with T cells." This rejection is also respectfully traversed. Claims 22 and 31 are

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believed patentable over these references, either alone or in combination, for the reasons set out below.

The Lampson and Williams references have been thoroughly discussed in the subject application or in other applications by the same Applicants currently pending before the same Examiner (e.g. Serial No. 100,072, filed December 4, 1979); it is believed that all of the obviousness implications of these two references were thoroughly dealt with in Applicants' previous responses. This was especially believed to be the case since neither Williams nor Lampson was referred to in the intervening Official Action. Nevertheless, for the record, Applicants wish to make the following comments regarding Williams and Lampson, which comments are substantially identical to those which overcame these references when they were raised in the related applications.

The Lampson reference teaches the use of the spleen fragment culture technique to produce antibodies, in which technique the spleen cells are obtained from mice which have been immunized with human lymphoblastoid cell lines. The lymphoblastoids cell lines were also used for screening of the resulting spleen fragment cultures. Thus, this reference merely discloses an alternate technique to the hybridoma method, without adding anything to the art of record.

No antibodies were obtained by Lampson (or even suggested) which have the characteristics of those claimed herein. In response to the specific statement by the Examiner, Lampson does <u>not</u> show hybridoma preparation, but rather the culturing of spleen fragments. Moreover, Lampson does <u>not</u> show the production of antibodies which are specific for <u>normal</u> human T cells. The antibodies which Lampson obtained react

with a malignant human T cell line and (in many cases) also with a malignant human B cell line. Thus, the manifold differences between the antibodies disclosed by Lampson and those claimed herein would appear to preclude the obviousness rejection under discussion.

The Williams reference teaches the immunization of mice with rat thymocyte membrane. This reference reports the same work described in the White reference (reference Y), previously discussed. As indicated in the discussion of the White reference, both White and Williams do not suggest the preparation of antibodies to human cells, let alone human T cells. Moreover, as previously discussed, the White reference indicates at page 671 the lack of practical result of this work. It is therefore not seen how the Williams reference can possibly be considered to render the claimed antibodies obvious.

As stated by Applicants' Attorney during the interview, it is clear from current knowledge in the biological arts that antibodies which react with rat T cells will not specifically react with human T cells.

The final reference under discussion is the McMichael reference, newly presented. This reference describes the results of immunizing mice with human thymocytes and the use of spleen cells from these immunized mice to produce hybridomas. As a result of this experiment, McMichael and his coworkers obtained an antibody which was highly specific for human thymocytes. They characterize the antigen with which this antibody reacts in the first full paragraph at page 209 of the article, in which they state:

"This antigen is, as far as we can tell, expressed exclusively on human thymocytes. No binding of [the antibody] was detectable on other lymphoid cells including peripheral T lymphocytes [T cells] and bone marrow cells. (emphasis added)"

In view of this statement, it is not seen how the Examiner can make the subject obviousness rejection. The antibody produced by McMichael does not react with peripheral T cells (perhipheral T lymphocytes), reacting exclusively with human thymocytes. Thus, McMichael does not teach or suggest the claimed antibody, which specifically reacts with essentially all normal human peripheral T cells, and therefore does not render obvious claims 22 and 31.

Since all of the claims now in the application are believed allowable, a Notice of Allowance is earnestly solicited.

C. Conclusion

For the reasons presented above, it is respectfully submited that Claims 22 and 31 are allowable, and such action is earnestly solicited.

Respectfully submitted,

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Name of applicant, assignee, or Registered Representative

(Signature)

April 8, 1982
(Date of Signature)

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1. (amended) A monoclonal antibody of class IgG produced by a hybridoma formed by fusion of cells from a mouse myeloma line and spleen cells from a mouse previously immunized with human T cells [and cells from a mouse myeloma line], which antibody:

a) reacts with essentially all normal human peripheral T cells and cutaneous T lymphoma cells, but not with normal human peripheral B cells, null cells or macrophages;

b) reacts with from about 5% to about 10% of normal human thymocytes;

c) reacts with leukemic cells from humans with T cell chronic lymphoblastic leukemia but does not react with leukemic cells from humans with T cell acute lymphoblastic leukemia, null cell acute lymphoblastic leukemia, or B cell chronic lymphatic leukemia;

d) reacts weakly with the human T cell line HJD-1 but does not react with CEM, Laz 191, or HM1;

e) does not react with the Epstein-Barr virus-transformed human B cell lines Laz 007, Laz 156, Laz 256, or SB; and

f) fixes complement.

2. The monoclonal antibody of Claim 1 which is of subclass IgG_2.

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3. The monoclonal antibody of Claim 1 which is produced from a hybridoma formed by fusion of P3X63Ag8U1 myeloma cells and spleen cells from a CAF_1 mouse previously immunized with E rosette purified human T cells.

15. A method for preparing monoclonal antibody which:

a) reacts with essentially all normal human peripheral T cells and cutaneous T lymphoma cells, but not with normal human peripheral B cells, null cells or macrophages;

b) reacts with from about 5% to about 10% of normal human thymocytes;

c) reacts with leukemic cells from humans with T cell chronic lymphoblastic leukemia but does not react with leukemic cells from humans with T cell acute lymphoblastic leukemia, null cell acute lymphoblastic leukemia, or B cell chronic lymphatic leukemia;

d) reacts weakly with the human T cell line HUD-1 but does not react with CEM, Laz 191, or HM1;

e) does not react with the Epstein-Barr virus-transformed human B cell lines Laz 007, Laz 156, Laz 256, or SB; and

f) fixes complement,

which comprises the steps of:

i) immunizing mice with E rosette positive purified human T cells;

ii) removing the spleens from said mice and making a suspension of spleen cells;

iii) fusing said spleen cells with mouse myeloma cells in the presence of a fusion promoter;

iv) diluting and culturing the fused cells in separate wells in a medium which will not support the unfused myeloma cells;

v) evaluating the supernatant in each well containing a hybridoma for the presence of the desired antibody;

vi) selecting and cloning hybridomas producing the desired antibody; and

vii) recovering the antibody from the supernatant above said clones.

16. The method of Claim 15 wherein said mice are of strain CAF_1 and said myeloma cells are P3X63Ag8U1.

17. (amended) A method for preparing monoclonal antibody which:

a) reacts with essentially all normal human peripheral T cells and cutaneous T lymphoma cells, but not with normal human peripheral B cells, null cells or macrophages;

b) reacts with from about 5% to about 10% of normal human thymocytes;

c) reacts with leukemic cells from humans with T cell chronic lymphoblastic leukemia but does not react with leukemic cells from humans with T cell acute lymphoblastic leukemia, null cell acute lymphoblastic leukemia, or B cell chronic lymphatic leukemia;

d) reacts weakly with the human T cell line HJD-1 but does not react with CEM, Laz 191, or HM1;

e) does not react with the Epstein-Barr virus-transformed human B cell lines Laz 007, Laz 156, Laz 256, or SB; and

f) fixes complement,

which comprises the steps of:

i) immunizing mice with E rosette positive purified human T cells;

ii) removing the spleens from said mice and making a suspension of the spleen cells;

iii) fusing said spleen cells with mouse myeloma cells in the presence of a fusion promoter;

iv) diluting and culturing the fused cells in separate wells in a medium which will not support the unfused myeloma cells;

v) evaluating the supernatant in each well containing a hybridoma for the presence of the desired antibody;

vi) selecting and cloning hybridomas producing the desired antibody;

[vii) recovering the antibody from the supernatant above said clones;]

viii) transferring said clones intraperitoneally into mice; and

ix) harvesting the malignant ascites or serum from said mice[.], <u>which ascites or serum contains the desired antibody.</u>

18. The method of Claim 17 wherein said mice are of strain CAF_1 and said myeloma cells are P3X63Ag8U1.

22. Mouse complement-fixing monoclonal antibody which reacts with essentially all normal human peripheral T cells but not with normal human peripheral B cells, null cells, or macrophages.

23. A method of preparing complement-fixing monoclonal antibody which reacts with essentially all normal human peripheral T cells but not with normal human peripheral B cells, null cells, or macrophages, which comprises culturing the hybridoma ATCC CRL 8001 in a suitable medium and recovering the antibody from the supernatant above said hybridoma.

24. A method of preparing complement-fixing monoclonal antibody which reacts with essentially all normal human peripheral T cells but not with normal human peripheral B cells, null cells, or macrophages, which comprises injecting into a mouse the hybridoma ATCC CRL 8001 and recovering the antibody from the malignant ascites or serum of said mouse.

25. A method for preparing complement-fixing monoclonal antibody which reacts with essentially all normal human peripheral T cells but not with normal human peripheral B cells, null cells, or macrophages, which comprises the steps of:

i) immunizing mice with E rosette positive purified human T cells;

ii) removing the spleens from said mice and making a suspension of the spleen cells;

iii) fusing said spleen cells with mouse myeloma cells in the presence of a fusion promoter;

iv) diluting and culturing the fused cells in separate wells in a medium which will not support the unfused myeloma cells;

v) evaluating the supernatant in each well containing a hybridoma for the presence of antibody to E rosette positive purified T cells;

vi) selecting and cloning a hybridoma producing antibody which fixes complement and reacts with essentially all normal human peripheral T cells but not with normal human peripheral B cells, null cells, or macrophages; and

vii) recovering the antibody from the supernatant above said clones.

26. A method for preparing a complement-fixing monoclonal antibody which reacts with essentially all normal human peripheral T cells but not with normal human peripheral B cells, null cells, or macrophages, which comprises the steps of:

i) immunizing mice with E rosette positive purified human T cells;

ii) removing the spleens from said mice and making a suspension of the spleen cells;

iii) fusing said spleen cells with mouse myeloma cells in the presence of a fusion promoter;

iv) diluting and culturing the fused cells in separate wells in a medium which will not support the unfused myeloma cells;

v) evaluating the supernatant in each well containing a hybridoma for the presence of antibody to E rosette positive purified T cells;

vi) selecting and cloning a hybridoma producing antibody which fixes complement and reacts with essentially all normal human peripheral T cells but not with normal human peripheral B cells, null cells, or macrophages;

vii) transferring said clones intraperitoneally into mice; and

viii) harvesting the malignant ascites or serum from said mice, which ascites or serum contains the desired antibody.

27. The monoclonal antibody prepared by the method of Claim 23.

28. The monoclonal antibody prepared by the method of Claim 24.

29. The monoclonal antibody prepared by the method of Claim 25.

30. The monoclonal antibody prepared by the method of Claim 26.

31. A complement-fixing monoclonal antibody of class IgG produced by a hybridoma formed by fusion of cells from a mouse myeloma line and spleen cells from a mouse previously immunized with human T cells which reacts with essentially all normal human peripheral T cells but not with normal human peripheral B cells, null cells, or macrophages.